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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,248	ROGAN ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 34-42 have been withdrawn.

DETAILED ACTION

Newly amended claims 43-54 are under consideration.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/27/2007 has been entered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 43-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening a human individual for cytogenetic abnormalities, it does not reasonably provide enablement for how to make and use probe that will produce hybridization probes that indicate cytogenetic abnormalities or chromosomal imbalances in "any" individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method for screening "any" individual for cytogenetic abnormalities by the use of probes occurring in within 1500kb of the terminal nucleotide. "Any " individual broadly encompasses humans, dog, cats, mice whale, etc.

The claims are further drawn delineating the extent of a chromosome imbalance in "any" individual by use of at least one hybridization probe located within 1500kb of the terminal nucleotide of the chromosome arm.

The claims are further drawn to associating the hybridization patterns with a specific clinical abnormality, including, idiopathic mental retardation, mental retardation or at least one other clinical abnormality, or mental retardation and cancer.

The claims are further drawn to the probes being represented at a single genomic location so that a "single hybridization signal" is detected.

The claims are drawn to detecting "any" cytogenetic abnormality. Any cytogenetic abnormality broadly encompasses deletions, insertions, translocations, duplications, trisomy.

The amount of direction or guidance

The specification teaches that telomeres are specialized protein-DNA structure that demaracate the end of each chromatid in a chromosome (see page 2, lines 21-23). The specification further teaches that telomeres are not chromosome specific and detection is difficult (see page 2, lines 25-30). The specification further teaches that the telomeres of vertebrates are made of repeats of $(TTAGGG)_n$. The specification further teaches that small rearrangements occur at the end of chromosomes resulting in clinical abnormalities including mental retardation, spontaneous abortion etc.

The specification further teaches in normal individuals there are 2 copies of a sequence and 2 sites of hybridization (see page 4, lines 12-14).

The specification many probes are known for FISH analysis of chromosomes, although the exact sequence and location have not been accurately determines (see page 6, lines 10-14). Further the specification teaches that many conventional FISH

probes contain telomeric DNA and thus are found to hybridize to many internal sequences in chromosome (see page 6, lines 20-25). The specification further teaches due to lack of knowing the sequence and the exact location of the probes would not allow the artisan to predictably determine cytogenetic abnormalities (see page 7, lines 10-20). The specification further teaches that de to this weakness and the high potential for a false negative the probes are unpredictable for diagnostic purposes (see page 7, lines 15-20). Further the specification teaches many currently available probes are know to cross react with other location (see table, page 8).

The specification further teaches most techniques are not sensitive enough to detect balanced translocation (see page 10, line 25).

The specification further teaches that the probes are based on the human genome and become more accurate (predictable) as more data is determined (see page 14, 1st paragraph). The specification further teaches a method of making single copy probes, although the claims are not limited to this method.

The specification further teaches that current probes and method were not reproducible (see page 19, lines 13-15) due to variable binding of repetitive sequences.

The specification further teaches chromosomal abnormalities were detected in ~0.5 % of patients with mental retardation and ~5% of patients with moderate to sever mental retardation (see page 20, lines 2-4).

The specification in Table 1 list a number of probes to specific subtelomeric regions but teach the sequences. The specification appears to teach in Table 2 the primer sequences and locations of the probes of Table 1, it is noted that only the primer

sequences are taught and thus the sequence of the whole probe does not appear to be known.

The specification further teaches use of said probes in figure 1-15 and 18-19.

Presence and absence of working examples.

The specification does not any working examples of non-human individuals assayed for cytogenetic abnormalities.

The specification does not provide working examples in which a representative number of cytogenetic abnormalities are detected. The specification teaches one example of a translocation in figure 18, however this is not representative of deletions, insertions, translocations, duplications, trisomy.

The specification contains no working examples in which chromosome imbalance was correlated with a disorder such as idiopathic mental retardation or cancer.

The state of prior art and the predictability or unpredictability of the art:

Rogan et al teaches methods of detecting chromosome imbalances and cytogenetic abnormalities in humans Rogan, et al (Genome Research, 2001, volume 11, pages 1086-1094).

Carter et al (Cytometery (2002) volume 49, pages 43-48) teaches the results of a workshop on detection of cytogenetic abnormalities by probe hybridization (see abstract). Carter et al teaches, "Few groups produced quantitative array hybridization data of quality, whereas the majority achieved a lower standard" (see abstract results). Carter et al thus teaches quantitative results were not predictable in this method. Carter further teaches hybridization results were more quantitative depending on the

hybridization procedure. Carter specifically teaches hybridization using gentle rocking was more effective than hybridization under cover slips or automated hybridization approaches.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish probes and methods that would result in a predictable hybridization pattern that would allow detection of cytogenetic abnormalities or chromosomal imbalances in "any" individual. This would be replete with trial and error experimentation because while the specification teaches representative probes, the claims are drawn to "any" probe. As the specification and art teaches that probes do not predictably detect cytogenetic abnormalities it would be unpredictable to associate the hybridization of "any" probe with cytogenetic abnormalities. Thus the skilled artisan would have to determine by trial and error experimentation, which probes and methods allow for reproducible detection of chromosome imbalance and cytogenetic abnormalities.

The specification and claims do not adequately set forth a structure function relationship for how probes within 1500kb of the terminal nucleotide predictably result in detection of "any" cytogenetic abnormalities. The claimed method would allow predictable determination of only deletions, insertions, translocation of the areas to which the probes hybridize. Thus the probes would not predictably allow determination

of "any" cytogenetic abnormality, specifically the claimed method could not detect any cytogenetic abnormality that does not encompass the specific probe sequences.

Further the skilled artisan would have to determine how to design probes that would detect cytogenetic abnormalities in "any" individual. The specification teaches primers for the synthesis of probes for human individuals, the specification and art are silent as to how to make and use probes in other species including-dog, cat, mouse, whale, etc. This would require trial and error experimentation as the probes of the specification are based on known sequences while the genome of the dog, cat, whale, etc have not been fully sequenced.

The skilled artisan would further have to determine which probes and banding patterns would be indicative of clinical abnormalities in any individuals. This would be replete with unpredictable trial and error experimentation as it is unclear how to diagnose mental retardation, idiopathic mental retardation, etc in dogs, cats, whales, etc.

As the claims recite "said probes being representing at a single genomic location or where paralogous sequences are closely linked so that a single hybridization signal is detected" would result in unpredictable experimentation. The specification and art teach design and probes that hybridize to a single chromosomal location, but that encompasses 2 hybridization signals in a genome, once on each pair. Alternatively, one could have a single signal if one of the two alleles were deleted, but in any genome that has both alleles would not be covered by the claims. Alternatively the claims could be to just probes of the X or Y chromosomes in humans and used to diagnose only

men. Since women have two Y chromosomes. Thus the specification and art do not predictably teach one of ordinary skill in the art to make probes that will predictably hybridize to a single genomic location resulting in a single hybridization signal being detected.

Claims 49-54 are drawn to detection of chromosomal imbalance, while claim 50 is drawn to correlating the imbalances to medical conditions. This would be unpredictable in that the claims do not require an individual but could be drawn to detecting chromosomal imbalances in a single chromosome in a single cell organism that cannot be mentally retarded or have cancer. Further the claims can broadly be drawn to the detection of chromosomal imbalance in a yeast artificial chromosome or bacterial artificial chromosome and thus it would further be unpredictable to associate chromosome imbalances with medical conditions with artificial chromosome produced in a laboratory.

Further, the Carter teaches that possession of the probes is not enough to make such hybridization assays predictable, but the method of hybridizing is also essential to reproducibility. Thus the skilled artisan would further have to determine hybridization conditions that would allow for reproducible data. This would require unpredictable trial and error experimentation as Carter teaches many labs could not produce quantitative data.

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable

experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

3. Claims 43-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 43-54 encompass the detection of a cytogenetic abnormality or chromosomal imbalance in "any" individual by use of "any" probe within 1500kb of the terminal nucleotides. Claim 45 further draws the claims to probes that hybridize to a single genomic location so that only a single hybridization signal is detected. The claims further draw the probe to probes having a length of less than 25 kb. The claims do not set forth any other structural requirements for probes.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification teaches the probes are directed to any single copy 1.8 kb interval with in 100kb of a telomeric sequence. This broadly encompasses any 1.8 kb sequence within 100kb of a telomere in any species, which is an enormous genus of nucleic acids.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The instant specification teaches primers to synthesize probes to chromosomes 1-13 in humans. The specification does not teach the sequence of any probes.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides that the nucleic acid be less than 25 kb and correspond to a 1.8kb fragment that is a single copy interval in any genome. This constitutes an enormous genus of nucleic acids. The specification however does not teach the sequence of these probes or probes to any other species, although the claims are broadly drawn to any individual. These the specification teaches probes to 13 chromosome while the claims broadly encompass chromosomes in every species, this is thousands.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen

Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a probe, without any definition of the particular probes claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

In the instant application, the provided information regarding nucleic acid probes to 13 human chromosomes, does not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed probes to chromosomes in “any” individual. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding probes for detecting cytogenetic abnormalities is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules claimed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 43-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 43-48 recite, "said hybridization occurring within 1500 kb of the terminal nucleotide." It is unclear if the terminal nucleotide is the last nucleotide in the gene, the chromosome, the probe, etc.

Claim 48 recites "said cytogenetic abnormalities being selected from the group consisting of idiopathic mental retardation, or mental retardation and at least one other clinical abnormality, or mental retardation and cancer, or combinations thereof." Claim 48 is indefinite in that idiopathic mental retardation, or mental retardation and at least one other clinical abnormality, or mental retardation and cancer and diseases and not cytogenetic abnormalities. These rejection can easily be overcome by amending the claim to recite, "cytogenetic abnormalities are correlated with diseases selected from..."

Claim 50 is indefinite in that it is drawn to correlating chromosomal imbalance with medical conditions. However, claim 49 does not require the chromosome to come from a subject individual, etc. Thus claim 50 can be drawn to correlating imbalances in bacterial artificial chromosomes, yeast artificial chromosomes, corn chromosome with mental retardation or cancer. It is unclear if these species have cancer or mental retardation.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Rogan, et al (Genome Research, 2001, volume 11, pages 1086-1094).

With regards to claim 43, Rogan et al teaches screening an individual for cytogentic abnormalities using probe fragments labeled by nick translation (see page 1092, 2nd column, last paragraph). The nick translation of Rogan results in plurality of probes. Rogan et al further teaches hybridization of the probes to fixed chromosomal preparations. Chromosomal preparation are the genome of an individual (see page 1092, 2nd column, last paragraph). Rogan et al teaches the use of CDC2L1, MAGEl2, HIRA probes for the detection of cytogenetic abnormalities (see Table1). The CDC2L1 probes are in the 1p36 region and within 1500 kb of the terminal nucleotide of

chromosome arm. MAGEI2, HIRA probes are within 1500 kb of the terminal nucleotide of each gene. Rogan teaches the probes of his invention detect known chromosome abnormalities, (see page 1090, 1st column, last paragraph). Rogan et al thus teaches a method of screening an individual for a cytogenetic abnormality using a plurality of probes, causing the probes to hybridize with the genome of an individual, said hybridization occurring with 1500kb of the terminal nucleotide.

With regards to claim 44, Rogan teaches altered hybridization of the HIRA probe to genomic DNA led to the detection of Degeorge's syndrome (see page 1090, column 2, 1st paragraph). Rogan et al further teaches that deletions of CDC2L1 results in Prader-Willi syndrome. Rogan et al thus teaches associating a hybridization pattern with specific clinical abnormalities.

With regards to claim 45, Rogan teaches the probes of his method are single copy probes (see page 1086, lines 4-19). Rogan demonstrates that his probe only hybridize to a single genetic location in figure 4. Rogan et al thus teaches his probes represent a single genetic location sot that a single hybridization single is detected.

With regards to claim 46, the sequence of Rogan's probes are known as exemplified by his teachings of accession numbers (see table1).

With regards to claim 47, Rogan teaches his probes are between 2 kb and 10kb (see page 1086, lines 4-9). Rogan thus teaches probes less than 25 kb.

With regards to claim 48, Rogan teaches his probes detect mutations in 1p36 which results in 1p36 and Prader-Willi, Angelman and DiGeroge Syndromes.

With regards to claim 49, Rogan et al teaches a method of using probes located within 1500kb of the terminal nucleotide of a chromosome (CDC2L1) for assaying subtelomirc regions of the chromosome to detect chromosomal imbalances to delineate the extent of chromosomal imbalance. Rogan teaches his method expands the repertoire of probes available for molecular genetic analysis of chromosomal alteration, probes delineate multigene family members, identify and size marker chromosome abnormalities.

With regards to claim 50, Rogan et al teaches that deletions of CDC2L1 results in Prader-Willi syndrome. The deletion of Rogan would result in a chromosomal imbalance and Prader Willi Syndrome is a form of idiopathic mental retardation.\

With regards to claim 51, Rogan et al teaches his probes were synthesized by nick translation and thus are a plurality of probes.

With regards to claim 52, Rogan teaches the probes hybridize to a specific chromosome arm (see Table 1).

With regards to claim 53, the sequence of Rogan's probes are known as exemplified by his teachings of accession numbers (see table1).

With regards to claim 54, Rogan teaches his probes are between 2 kb and 10kb (see page 1086, lines 4-9). Rogan thus teaches probes less than 25 kb.

Response to arguments

The response asserts that Rogan does not teach probes within 1500kb of the terminal nucleotide. This response has been thoroughly reviewed but is not considered persuasive because the CDC2L1 probe is within 1500Kb of the terminal nucleotide.

Further the terminal nucleotide of a chromosome changes due to aging of the cell, proliferation, etc. The skilled artisan would thus be unable to accurately determine which the exact distance of any probe from any terminal nucleotide.

7. Claims 43-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Flint, et al (Nature Genetics, 1995, volume 9, pages 132-140).

With regards to claim 43, Flint et al teaches fluorescence in situ hybridization (FISH) labeled by nick translation (see page 139 first column fluorescence in situ hybridization) and detection of a deletion of 13q region in patient AH, while no deletion was found in parent (see page 133, 2nd column lines 19-24and figure 2b). Patient AH has idiopathic mental retardation (page 133, column 1 line 8). Nick translation results in multiple probes of less then 25 kb. Flint et al teaches the probes of table 1 which are within 1500kb of the terminal nucleotide. The deletion taught by Flint demonstrates a chromosome 13q imbalance, which is a cytogenetic abnormality. The method of flint thus detects cytogenetic abnormalities by hybridization patterns in an individual by hybridization with probes that hybridize within 1500kb of the terminal nucleotide.

With regards to claim 44, Flint et al teaches these abnormalities of the 22q and 13q locus was found in only mentally retarded individuals, but not normal controls. Flint thus teaches associating the hybridization with clinical abnormalities.

With regards to claim 45, Flint teaches southern blot analysis which demonstrates that only a single genomic location (single band) is detected (see Figure 1).

With regards to claim 46, the nick translation of Flint results in a plurality of probes which have known sequences as the restriction site at which the probes are cleaved are known.

With regards to claim 47, the nick translation of Flint results in probes of less that 25 kb.

With regards to claim 49, Flint et al teaches fluorescence in situ hybridization (FISH) labeled by nick translation (see page 139 first column fluorescence in situ hybridization) and Southern blotting for detection of a deletion of 13q region in patient AH, while no deletion was found in parent (see page 133, 2nd column lines 19-24 and figure 2b). Patient AH has idiopathic mental retardation (page 133, column 1 line 8). Nick translation results in multiple probes of less then 25 kb. Flint et al teaches the probes of table 1 which are within 1500kb of the terminal nucleotide. The deletion taught by Flint demonstrates a chromosome 13q imbalance, which is a cytogenetic abnormality. The method of Flint thus delineates the extent of chromosomal imbalances by hybridization patterns in an individual by hybridization with probes that hybridize within 1500kb of the terminal nucleotide.

With regards to claim 50, Flint teaches detecting deletions in chromosome that are chromosomal imbalances that are found only in patients with idiopathic mental retardation. Flint thus teaches correlating imbalances with a medical condition of idiopathic mental retardation.

With regards to claim 51, the nick translation of Flint results in a plurality of probes which have known sequences as the restriction site at which the probes are cleaved are known.

With regards to claim 52, the Southern blot of Flint figure 1 teaches the probes bind to a specific chromosome sequence and thus arm.

With regards to claim 53, Flint teaches the probes were cleaved by specific restriction enzymes and thus have known sequences.

With regards to claim 54, the nick translation of Flint results in probes of less that 25 kb.

Response to Arguments

The response asserts that Flint does not teach any probes within 1500kb of the terminal nucleotide. This argument has been thoroughly reviewed but is not considered persuasive because the probes of Flint are within 1500 kb of the terminal nucleotide. For example all of the probes depicted in figure in figure 1 are within 1500kb of the terminal nucleotide of the chromosome they hybridize to as the chromosome have been cleaved and thus all the fragments of the southern blot are less than 1500 kb. Further the terminal nucleotide of an intact chromosome is highly variable as the telomere length varies over the life time of the individual and between individuals. Further mutations, deletions and translocation would further alter the distance of the probe from the terminal nucleic acid.

1. Claims 43-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Bentz et al (Blood, 1994, volume 83 pages 1922-1928).

With regards to claim 43, Bentz teaches hybridization of nick translated YAC-probe D107F9, results in 2 hybridization signals from normal cells and 3 signals from BCR-ABL cells (see page 1923, column 2, lines 1-4and figures 1 and 2). Nick translation results in a plurality of short probes, all less then 25 kb. Bentz further teaches the 2 signals in normal cells are due to hybridization to chromosome 22 (see page 1923, column 2, lines 4-6 and figures 1) and the third signal is due to a translocation of chromosome 22 to chromosome 9q. Bentz teaches the BCR-ABL translocation detected by the D107F9 is indicative of CML or Ph-positive ALL (see abstract). Bentz thus teaches a method of screening individuals with cancer for cytogenetic abnormalities using a probe of less then 25 kb. The hybridization pattern of the probes is indicative of cytogenetic abnormalities.

With regards to claim 44, Bentz teaches these abnormalities are associated with leukemia, which is a cancer and a specific clinical abnormality.

With regards to claim 45, Bentz further teaches the 2 signals in normal cells are due to hybridization to chromosome 22 (see page 1923, column 2, lines 4-6 and figures 1). Thus the probes are specific to a single genomic location.

With regards to claim 46, Bentz teaches the probes were amplified with primers of known sequence which are known. The sequence of at least the sequence to which the primers hybridize is known. Thus Bentz teaches a method using a plurality of probes with a known sequence.

With regards to claim 47, the probes of Bentz are made by nick translation which inherently produces a plurality of probes that are less than 25 kb.

With regards to claim 49, Bentz teaches the D107F9 probe hybridization detects an imbalance in both chromosome 22 and 9 of the BCR-ABL positive cells (see page 1923, column 2, lines 1-4and figures 1 and 2). These imbalances are associated with ALL and CML, which are specific clinical abnormalities.

With regards to claim 50, Bentz teaches the chromosome imbalance is associated with leukemia, which is cancer.

With regards to claim 51, the probes of Bentz are made by nick translation which inherently produces a plurality of probes.

With regards to claim 52, Bentz et al teaches the probes are specific to chromosomes 9 and 22.

With regards to claim 53, Bentz teaches the probes were amplified with primers of known sequence which are known. The sequence of at least the sequence to which the primers hybridize is known. Thus Bentz teaches a method using a plurality of probes with a known sequence.

With regards to claim 54, Bentz teaches the probes are made by nick translation and thus the probes have a length of less than 25 kb.

Response to Arguments

The response assert that Bentz does not teach probes within 1500kb of the terminal nucleotide. This argument has been thoroughly considered, but is not found persuasive because the probes of Bentz span the translocation breakpoint of the chromosome 9 and 22 translocation. Thus the probes of Bentz are within 1500 kb of

the terminal end of chromosome 9 and 22 in the translocated Philadelphia chromosome are within 1500 kb of the translocation point and thus the terminal end of the chromosome. Further the terminal nucleotide of an intact chromosome is highly variable as the telomere length varies over the life time of the individual and between individuals. Further mutations, deletions and translocation would further alter the distance of the probe from the terminal nucleic acid.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 43-45, 49 and 51are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No.

7014997. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are co-extensive in scope.

Claim 43 of instant application is drawn to a method of screening individuals with clinical abnormalities with a plurality of probes. The hybridization of said probes resulting in patterns indicative of cytogenetic abnormalities. Claim 3 of '997 patent teaches the detection of hybridization pattern for detection of cytogenetic abnormalities. Claim 1 of '997 patent teaches chromosome abnormalities are indicative of pathological abnormalities.

Claim 44 of instant application is drawn to associating hybridization patterns of probes with clinical abnormalities. Claim 1 of '997 patent teaches hybridization is indicative of pathological conditions.

Claim 45 of instant application is drawn to probes hybridizing to a single genomic location. Claim 1 of '997 patent teaches a nucleic acid probe complementary to a non-repetitive portion of genome. A non-repetitive portion of the genome would result in probes hybridizing to a single genomic location.

Claim 49 of instant application is drawn to detecting and delineating the extent of chromosome imbalances by comparison of probe hybridization to a standard genome map. Claim 1 of '997 patent teaches hybridization of nucleic acid of non-repetitive sequence probes with known genomic sequence coordinates. The hybridization of probes from claim 1 of '997 patent detect chromosome imbalances and since known genomic coordinates are known to delineate extent by comparison to standard genomic map.

Claim 51 of instant application is drawn to a method of utilizing a plurality of probes. Claim 1 of '997 patent teaches the use of a pair of probes, which is a plurality.

Response to Arguments

The response assert that '997 does not teach probes within 1500kb of the terminal nucleotide. This argument has been thoroughly considered, but is not found persuasive because the probes of '997z span the translocation breakpoint of the chromosome 9 and 22 translocation. Thus the probes of '997 are within 1500 kb of the terminal end of chromosome 9 and 22 in the translocated Philadelphia chromosome are within 1500 kb of the translocation point and thus the terminal end of the chromosome. Further the terminal nucleotide of an intact chromosome is highly variable as the telomere length varies over the life time of the individual and between individuals. Further mutations, deletions and translocation would further alter the distance of the probe from the terminal nucleic acid.

Summary

No claims are allowed over prior art cited.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Carla Myers/
Primary Examiner, AU 1634